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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/047,068	04/16/93	WEINBERG	I 20029300646

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1806	26

18M2/0217

NIXON AND VANDERHYE, P.C.
1100 NORTH GLEBE RD., 8TH FL.
ARLINGTON, VA. 22201-4714

DATE MAILED: 02/17/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 12/29/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☐ Claims 8-15 are pending in the application.
   Of the above, claims 10,12 are withdrawn from consideration.
2. ☑ Claims 1-7 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 8, 9, 11, 13-15 are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 8-15 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. The Art Unit location and the examiner of your application in the PLO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

16. Claims 1-7 have been canceled.
Claims 8-15 are pending.

17. The following is a reiteration of the restriction requirement between the previous Examiner Davenport and the applicant's representative Wilson on 1/27/95.

Upon reconsideration, the finality of the rejection of claims 8-15 in the Office action of April 20, 1994 is withdrawn in view of the following new election/restriction requirement.

Claim 9 is generic to a plurality of disclosed patentably distinct species comprising Group I: anti-CD44 antibody; Group II: soluble CD44; Group III CD44: oligopeptides and Group IV: hyaluronate. Applicant is required to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

During a telephone conversation with Mary Wilson on 1/27/95, a provisional election was made with traverse to prosecute the invention of Group I, by selecting the species, anti-CD44 antibody (claims 8, 9, 11, 13-15). Affirmation of this election must be made by applicant in responding to this Office action. Claims 10 and 12 and the species of soluble CD44, CD44 oligopeptides and hyaluronate are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Upon reconsideration by the current examiner, the following restriction is in place.

Claim 9 is generic to a plurality of disclosed patentably distinct species comprising Group I: anti-CD44 antibody; Group II: soluble CD44 and CD44 oligopeptides and Group III: hyaluronate.

Since applicant selected Group I, drawn to CD44-specific antibodies, then the rejoining of previous Groups II and III do not affect the current claims and species under consideration.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

18. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825 (see the specification at page 9, Table 1). However, this application fails to comply with the requirements set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is required to fulfill these requirements.

Applicant is reminded to define the SEQ ID NOS in both the specification and claims.

19. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

20. Applicant should restrict the Abstract to the claimed invention.

21. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PLO-948. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes.

22. The disclosure is objected to because of the following informalities: page 10, line 37 - "cystein" should be "cysteine".

The use of the trademark "SEPHAROSE" has been noted in this application. It should be capitalized or accompanied by the ™ symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks

should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required.

The application is required to be reviewed and all spelling and trademark errors corrected.

23. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

Applicant has not disclosed how to use CD44-specific antibodies therapeutically in humans. There is insufficient information or nexus of the invention with respect to the in vitro or in vivo operability of claimed therapeutic strategy to inhibit CD44-facilitated entry of HIV into cells.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro inhibition of monocyte infection by a particular HIV strain accurately reflects the relative of the claimed therapeutic strategy.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as

adverse side effects prohibitive to the use of such treatment.

It has been well known in the art that retroviral infections in general, and HIV infections, in particular, are refractory to anti-viral therapies. Further, it has been well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al. (Clin. Exp. Immunol., 1992), clinical trials monoclonal antibodies therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference (see page 3, column 2, paragraph 3). Similarly, Hirsch et al. (N. Eng. J. Med., 1993) clearly teach that the success of translating [promising avenues of investigation into clinical practice has been meager (Page 1806, column 1, paragraph 2). For example, while soluble CD4 is a potent inhibitor of finding of certain strains of HIV-1 to CD4 cells in vitro, clinical HIV-1 isolates are less susceptible to such inhibition (page 1691, column 1, paragraph 2). Therefore, the art does recognize the benefit of even HIV-specific or CD4-specific (versus claimed CD44-specific) inhibitors can block HIV infection clinically.

Furthermore, it is noted that Rivaderneira et al. teach CD44-specific antibodies could inhibit the monocytotropic HIV-1-BaL infectivity of monocytic cells to some degree under certain culture conditions but could not block lymphocytotopic HIV-1 infection (manuscript filed with the 12/23/93 amendment, Paper No. 18). Guo et al. also teach anti-CD44 antibodies did not inhibit infection (see entire document, particularly page 2234, column 2, paragraph 1).

The claimed method utilizing CD44-specific antibodies appears limited to monocytic cells (versus lymphocytes) and does not completely inhibit infection of one HIV isolate in these cells under defined culture conditions. Therefore, it is not clear how the CD44-specific antibodies could inhibit HIV infection by various HIV strains in mixed leukocyte populations either in vitro or in vivo.

Concerning antibody therapy, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences.

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection. In a brief review of adhesion therapy, Shaffer relays such concerns about monoclonal antibodies, which are promising but involve toxicities and do not seem to have a lasting effect upon repeated use (Biotechnology Newswatch, 1993).

In the absence of clear and convincing evidence commensurate in scope with the allegations and claims, applicant has not provided convincing evidence that their claimed invention is indeed operable as a therapeutic or preventative for HIV infection and the claimed invention is deemed to lack operability.

Therefore it does not appear that the asserted operability of the claimed methods for inhibiting HIV infection by CD44-specific antibodies would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

B) It is apparent that the A3D8 and A1G3 antibodies are required to practice the claimed invention as disclosed in the specification and cited in the claims. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the appropriate hybridomas. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the A3D8 and A1G3 antibodies and they do not appear to be readily available materials. Deposit of the appropriate hybridomas would satisfy the enablement requirements of 35 U.S.C. 112.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions

imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

c) the deposit will be maintained for a term of at least thirty years and at least five years after the most recent request for the furnishing of a sample of the deposited material;

d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

25. Claims 1-8, 9, 11, 13-15 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see sections 23-24).

26. Claim 11 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite in the recitation of "A3D8" and "A1G3" because their characteristics are not known. The use of "A3D8" and "A1G3" monoclonal antibodies as the sole means of identifying the claimed antibodies renders the claim indefinite because these terms are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct cell lines or hybridomas.

The amendments must be supported by the specification so as not to add any new matter.

27. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

28. Claims 1-8, 9, 11, 13-15 are rejected under 35 U.S.C. § 103 as being unpatentable over Willerford et al. (J. Immunol., 1990) or Landay (U.S. Patent No. 5,108,904) in view of Nicholson et al. (J. Immunol., 1986) and Matsushita et al. (AIDS Res. Hum. Retrovir., 1990). Claims 1-8, 9, 11, 13-15 are drawn to the use of CD44-specific agents particularly antibodies to inhibit HIV infection.

Both Willerford et al. and Landay et al. teach that $CD44^+$ cells are a reservoir of HIV infection (see entire documents). These references differ from the claimed invention by not teaching to use CD44-specific antibodies per se to inhibit HIV infection.

Nicholson et al. teach that the infection of normal peripheral blood cells including monocytes occurs much more readily in co-cultivation assay as opposed to infection by cell-free virus (see entire document).

Matsushita et al. teach the use of immunotoxins to kill HIV-infected cells as well as the production of virions in T cells and macrophages in vivo (see entire document).

Therefore, the ordinary artisan would have been motivated at the time the invention was made to produce CD44-specific immunotoxins to kill HIV-infected cells as a means to reduce or eliminate HIV-infected cells. The ordinary artisan would have applied standard protocols known at the time the invention was made to produce CD44-specific immunotoxins as such cells appear to be reservoirs of HIV infection in vivo. There appears to no patentable distinction between the CD44-specific antibodies taught by the references and the A3D8/A1G3 antibodies claimed. By eliminating $CD44^+$ cells, one would inhibit the infection of monocytes as well, as indicated by the studies of Nicholson et al. above.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of CD44-specific antibodies as a therapeutic regimen in treating human HIV infection. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

It is noted that the instant claims are not limited to native antibodies, therefore CD44-specific immunotoxins do read on the claimed invention.

29. No claim is allowed.

30. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
February 15, 1995

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
2/16/95